	Mild AS PG mean <30 mm Hg	Moderate AS PG mean >30 mm Hg	Severe AS PG mean > 50 mm Hg	AV R	
n	11	18	39	17	
NT-proBNP (pg/ml)	676	1508	3311	854	P < 0,01
PG mean (mm Hg)	15,3	37,8	64,3	15,1	P < 0,01
LVM (gr)	215	245	271	199	P < 0,05
Ejection fraction (%)	54,1	51,1	49,3	55	n.s.

Conlusions: NT-proBNP was closely linked to severity of aortic stenosis and therefor may be usefull for therapeutical decision making.

1134-23

Is Mitral Regurgitation in Congestive Heart Failure Truly Functional? Evidence for Significant Biochemical Changes in the Valvular Extracellular Matrix

Kathryn J. Grande-Allen, Richard W. Troughton, Allen G. Borowski, Penny L. Houghtaling, Nicholas R. DiPaola, Christine S. Moravec, Ivan Vesely, Brian P. Griffin, The Cleveland Clinic Foundation, Cleveland, OH

Background: Mitral regurgitation (MR) is a complication for many patients with congestive heart failure (CHF). This MR was previously thought to be functional, due to alterations in the cardiac geometry rather than in the valvular microstructure. In contrast, we hypothesize that the geometric alterations found in CHF might be associated with biochemical changes in the extracellular matrix of the mitral valve.

Methods: Mitral valves were obtained post transplant from hearts with CHF (20 dilated cardiomyopathy, 14 ischemic, 3 other); all patients had undergone recent echocardiography. Left ventricular (LV) collagen and valvular DNA, collagen, glycosaminoglycan (GAG), and water content were measured, normalized to tissue weight, and compared with autopsy controls (n=12). Valvular and cardiac chamber dimensions and functional parameters were compared with biochemical parameters using a repeated measures generalized linear model.

Results: The mitral leaflets in CHF had 88% more DNA, 18% more GAGs, and 6% more collagen than normal ($p<0.05$). Mitral chordae in CHF had 83% more DNA, 42% more GAGs, and 8% less water ($p<0.05$). The elevated leaflet collagen concentration was significantly associated with increased anterior leaflet length and LV dimensions, and slightly associated with MR grade ($p=0.06$). Increased leaflet DNA, an indicator of cellularity, was associated with anterior leaflet thickening ($p=0.002$) and MR grade ($p=0.01$). Elevated leaflet GAGs were associated with left atrial diameter ($p=0.002$) and alterations in early and late diastolic flow ($p<0.05$). Chordal collagen, cellularity, and water concentrations were similarly associated with annular and ventricular dimensions as well as LV collagen concentration ($p<0.04$).

Conclusion: Mitral leaflets and chordae in CHF have significant biochemical differences from autopsy controls. These changes in the valvular extracellular matrix occur in proportion to the alterations in cardiac dimensions that accompany CHF. Our biochemical finding of leaflet and chordal remodeling suggests that MR in patients with CHF may not be purely functional, and that these mitral valves from failing hearts should not be considered "normal."

1134-24

Neurohormonal Activation Is Associated With Left Ventricular Remodeling in Chronic Asymptomatic Mitral Regurgitation and Normal Left Ventricular Ejection Fraction

Min Pu, Laurence M. Demers, Joseph Gascho, Hua Yang, John Boehmer, Benjamin C. Sun, Sanjay M. Mehta, Sanjay M. Mehta, Walter Pae, William Davidson, Jr., Hershey Medical Center, Hershey, PA

Background: Neurohormones are elevated in patients with chronic symptomatic mitral regurgitation (MR) and/or left ventricular (LV) dysfunction. There is little data regarding neurohormonal activation in asymptomatic MR with normal resting and exercise LV function.

Methods: We report our initial results of a prospective study. A total of 14 normal subjects and 7 asymptomatic MR patients were enrolled. Patients had at least 3+ MR, regurgitant orifice area of 0.43±0.12cm^2 and resting LV ejection fraction (LVEF) of 65±5.5%. Plasma epinephrine, norepinephrine, renin activity and N-terminal brain natriuretic peptide (N-BNP) were measured. Resting and stress exercise echocardiography were performed. LVEF, end-diastolic diameter (LVEDD), volume, end-systolic diameter and volume were measured. Exercise capacity was expressed as metabolic equivalents. **Results:** Although MR patients presented with normal resting LVEF and normal exercise response (increased LVEF, decreased LV end-systolic diameter with excellent exercise capacity-metabolic equivalents, 12±1.7), neurohormones were elevated, especially N-BNP (table). Significant LV remodeling was seen in the MR group with increased resting and post-exercise LV diameters and volumes. **Conclusions:** Neurohormones, especially N-BNP, are elevated in asymptomatic MR patients with apparently normal resting and exercise LV function, but dilated LV. Neurohormonal activation may indicate ongoing LV remodeling due to volume overload.

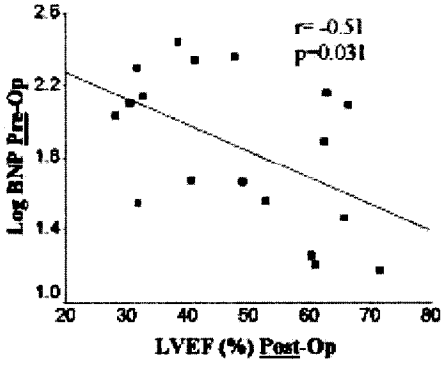
	Resting LVEDD (cm)	Resting LVEDV (ml)	Resting LVEF (%)	N-BNP (fmol/ml)	Epinephrine (nM)	Nor-Epinephrine (nM)	Renin (ng/ml/h)
Normal	4.7±0.6	80±15	66±5	291±82	1.2±0.3	3.3±0.6	0.74±0.7
MR group	5.5±0.6	164±29	65±5	435±113	1.5±0.5	3.6±0.9	1.7±2.0
P	<0.01	<0.001	>0.05	<0.01	=0.11	=0.44	=0.13

1134-25

B-Type Natriuretic Peptide Predicts Left Ventricular Response to Surgery in Patients With Severe Mitral Regurgitation in Asymptomatic Patients With Preserved Left Ventricular Function

W.H. Wilson Tang, Richard W. Troughton, Deborah A. Agler, Kathy Morris, Gary S. Francis, Jianxin Qin, Brian P. Griffin, The Cleveland Clinic Foundation, Cleveland, OH

Background: BNP has been validated as marker of cardiac function and prognosis in a variety of settings. To date, the relationship of pre- and post-op BNP to cardiac structure and function in asymptomatic patients with severe mitral regurgitation (MR) has not been well defined. **Methods**: We prospectively studied 22 consecutive asymptomatic patients (mean age 56 ±13 yrs) with severe MR and LV ejection fraction (EF) =55% referred for mitral valve surgery. Patients underwent pre- and post-op 2D echo evaluation, with concurrent sampling of BNP (Biosite). LV volumes and EF were calculated by biplane Simpson's method. Cardiac dysfunction was defined as EF <50%. **Results**: Mean pre-op data included: regurgitant orifice area = 0.88 ±0.4 cm^2, EF = 61 ±6%, LVEDV = 177 ±44 ml, LVESV = 69 ±23 ml. BNP increased acutely from 92 ±73 pg/ml to 314 ±200 pg/ml following surgery. Pre-op logBNP correlated significantly with pre-op LA volume ($r=0.49$, $p=0.04$), post-op LVESV ($r= 0.50$, $p=0.04$) and post-op EF ($r= 0.51$, $p=0.03$), but not with other echo measures. Pre-op BNP was higher in patients who developed post-op cardiac dysfunction (141 ±85 pg/ml vs 57 ±51 pg/ml, $p=0.03$). A pre-op BNP of 50 pg/ml had a sensitivity of 83%, specificity of 60%, and negative predictive value of 91% for prediction of a post-op cardiac dysfunction (C=0.8). **Conclusion**: Pre-op plasma BNP correlates significantly with post-op EF and LVESV in our study population. A pre-op plasma BNP below 50 pg/ml maybe useful in excluding the likelihood of post-op cardiac dysfunction.



1134-26

Serum B-Type Natriuretic Peptide in Patients With Chronic Mitral Regurgitation Is Not Elevated

Micah J. Eimer, Deborah Ekery, Vera Rigolin, Robert O. Bonow, William Cotts, Northwestern University Medical School, Chicago, IL

Background: Chronic mitral regurgitation (MR) imposes a progressive hemodynamic burden upon the left ventricle (LV). Management is based on symptoms and LV size and function. To determine if B-Type natriuretic peptide (BNP), a hormone secreted by ventricular myocytes under strain, may be a useful marker of ventricular deterioration, we measured BNP levels in patients with chronic MR.

Methods: We studied 9 patients with moderate to severe MR and a range of symptoms (mean age 45 ±16.6) and five normal control subjects (mean age 42.2 ±11.1) by 2D echocardiography with Doppler. LV ejection fraction (EF), LV end diastolic volume (EDV), end systolic volume (ESV), and LV mass index (LVMI) were measured and severity of MR was assessed semiquantitatively using color Doppler. Patients were excluded if they had any other valve lesion. BNP levels were measured by the Shionogi assay. **Results:** Patients and controls did not differ in age and had similar EF (63±12 vs 66±9%, p=ns). Seven of the 9 patients had severe MR and 6 had dyspnea, of whom 2 underwent valve surgery within 6 months. Compared to controls, the MR patients had significantly higher LVMI (109±30 vs 72±15 g/m^2, p=.02), ESV (53±25 vs 27±6 ml, p=.02) and EDV (132±42 vs 84±23 ml, p=.04). However, there was no significant difference in serum BNP levels (11±8 vs 6±4 pg/ml, p=0.20) between the two groups, and BNP did not relate to severity of MR or to symptoms.

Conclusion: These findings suggest that chronic MR is not associated with elevated lev-

els of B-Type natriuretic peptide despite significantly increased LV mass and volumes, even in patients with symptoms. Therefore, BNP may not be a useful marker in the management and evaluation of patients with chronic MR.

ORAL CONTRIBUTIONS

841 Clinical Markers Predictive of Outcome in Patients With Valvular Heart Disease

Tuesday, April 01, 2003, 8:30 a.m.-10:00 a.m.
McCormick Place, Room S101

8:30 a.m.

841-1 The Effective Regurgitant Orifice Area Is Predictive of Survival in Patients With Organic Mitral Regurgitation

Maurice L. Enriquez-Sarano, A. Jamil Tajik, David Messika-Zeitoun, Jean-Francois Avierinos, Michael Bellamy, Christophe Tribouilloy, Mayo Clinic, Rochester, MN

Background: Quantitation of mitral regurgitation (MR) is possible using Doppler-Echocardiography and allows measurement of the Effective Regurgitant orifice (ERO) area and of the Regurgitant volume (RVol). However, the implications of these measurements regarding survival after diagnosis are unknown because no long-term study outcome study has yet been conducted.

Methods: We prospectively enrolled 458 patients with MR due to organic mitral lesions (mitral prolapse in 360 or 79%) in whom quantitation of MR was obtained at baseline by at least 2 independent methods. The end-points analyzed were survival under conservative management and the combined end-point of death or mitral surgery.

Results: At diagnosis, age was 64±14 years and 61% were male. ERO was 41±28 mm2 (range 2 to 180 mm2) and RVol was 65±40 mL/beat (range 3 to 227). The left ventricular end-diastolic volume was enlarged at 107±28 mL/m2 and the ejection fraction was normal at 69±9%. The 5-year rates of mortality under conservative management and of surgery or death were 24±3% and 66±3%. Both ERO and RVol were univariately predictive of these end-points (P<0.001) but in multivariate analysis adjusting for age, sex, functional class and ejection fraction, only ERO was predictive of survival (RR 1.22 [1.06-1.38] per 10 mm2 increase, P=0.005). ERO was also independently predictive of death or mitral surgery (RR 1.41 [1.29-1.52] per 10 mm2 increase, P<0.001). 5 years after diagnosis, for patients with ERO<20, 20-30 and ≥30 mm3, mortality under conservative management was 9±3%, 31±10% and 49±8%, respectively and death or mitral surgery (excluding patients operated within 3 months of diagnosis) was 14±4%, 55±9% and 83±4%, respectively (both P<0.001).

Conclusion: The present study demonstrates for the first time in patients with organic MR, 1-the strong outcome implications of quantitative measures of degree of MR, 2-the preeminent independent prognostic value for survival of ERO area, which 3-allows to stratify patients into groups at low-, medium- and high-risk. Hence, measurement of ERO area of MR is an essential tool in management of patients with organic MR.

8:45 a.m.

841-2 Brain Natriuretic Peptide Predicts Severity of Aortic Stenosis

Johann Auer, Thomas Weber, Robert Berent, Elisabeth Lassnig, Josef Seier, Bernd Eber, General Hospital Wels, Wels, Austria

Background: Brain natriuretic peptide (BNP) and atrial natriuretic peptide (ANP) constitute a cardiac hormone system mediating natriuresis, diuresis, and vasodilation. Whereas ANP is secreted mainly from cardiac atria, BNP is produced to a larger extent in ventricles and has been shown to correlate with end-systolic wall stress in patients with aortic stenosis (AS). Echocardiography with doppler examination of the aortic valve provides a very accurate assessment of the trans-valvular aortic pressure gradient (TVPG) and is used to monitor progression of AS. This study evaluated circulating BNP as a marker of left ventricular hypertrophy and atrial pressure increase in patients with AS.

Patients and Methods: We investigated the serum concentrations of BNP by radioimmunoassay in 69 AS patients (35 males, mean age 70,9 years; range 37-90; mean TVPG determined by echocardiography 45,2 mmHg (+/- 20,6), calculated mean aortic valve area (AVA) (assessed invasively) 0,85 cm2 (+/- 0,3). TVPG were correlated to the AVA (r=0,54, P=0,001). Results are expressed as mean (+/- standard deviation), correlations were tested by Spearman-rang test and comparisons between group were tested by the Mann-Whitney test.

Results: BNP levels were significantly higher in AS patients with AVA less than 1 cm2 (2558,5 pg/ml; +/- 2555,6) when compared with the patients with AVA more than 1 cm2 (1567,4 pg/ml (+/- 2447,9) P=0,049). Moreover, BNP levels were increased in AS patients with TVPG of 50 (60,5 +/- 10,3) mmHg or more (4351,4 pg/ml; +/- 4699,5) in comparison to patients with TVPG less than 50 (29,9 +/- 16,6) mmHg (1373,8 pg/ml; +/- 2178,8, P=0,04). BNP levels were correlated to the TVPG and AVA (r=0.43 and r=0.52, P<0.001), respectively.

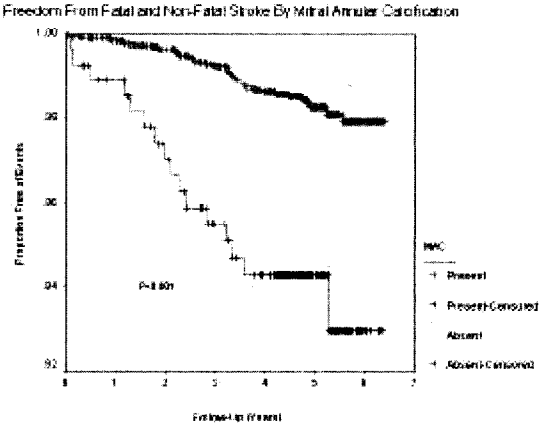
Conclusion: These results suggest BNP levels increase in relation to the TVPG and AVA. BNP measurement could potentially be used to monitor progression of disease non-invasively. This marker may also be useful to identify the optimum time for surgery in AS.

9:00 a.m.

841-3 Mitral Annular Calcification, Aortic Sclerosis, and Incident Stroke in American Indians Free of Clinical Cardiovascular Disease

Jorge R. Kizer, David O. Wiebers, Jack P. Whisnant, James M. Galloway, Thomas K. Welty, Elisa T. Lee, Lyle Best, Mary J. Roman, Richard B. Devereux, Weill Medical College of Cornell University, New York, NY, Mayo Clinic, Rochester, MN

While mitral annular calcification (MAC) & aortic sclerosis have been reported to be risk factors for cerebrovascular events, their relative prognostic significance independent of other echo predictors is uncertain. We investigated the predictive value of MAC & aortic sclerosis for incident stroke while accounting for other proven echo predictors. Our cohort comprised American Indians in the Strong Heart Study having echo in 1993-95. Exclusion criteria: coronary/valvular disease (aortic stenosis); prior stroke; atrial fibrillation; ejection fraction ≤ 35%; segmental wall motion abnormality. Follow-up was obtained through 12/99. N = 2859. Age = 58 y, women = 64%, hypertension = 54%, diabetes = 47%, cholesterol/HDL = 4.7, body-mass index = 31 kg/m^2, smoker = 31%, renal insufficiency = 2.3%, MAC = 10%, aortic sclerosis = 8%, left atrial index = 2.2 cm/m, LV mass index = 40 g/m$^{2.7}$. Incident strokes = 60. MAC, but not aortic sclerosis, was a significant univariable predictor of stroke (Figure). In Cox models adjusting for all above factors, MAC emerged as an independent predictor of stroke (RR 2.2, P = 0.028). Aortic sclerosis was not predictive whether or not MAC was considered. Our findings demonstrate MAC to be a strong predictor of stroke independent of other echo risk factors, & are in line with other studies showing that aortic sclerosis is not independently predictive of cerebral events. In patients without overt cardiovascular disease, the isolated presence of MAC warrants aggressive primary prevention.



9:15 a.m.

841-4 Does Aortic Valve Sclerosis Predict Cardiovascular Events Independently of Albuminuria in Hypertension? A LIFE Study

Michael H. Olsen, Kristian Wachtell, Jonathan N. Bella, Vittorio Palmieri, Eva Gerdts, Markku S. Nieminen, Gunnar Smith, Björn Dahlöf, Hans Ibsen, Richard B. Devereux, Glostrup University Hospital, Copenhagen, Denmark, The Weill Medical College of Cornell University, New York, NY

Background: Aortic valve (AV) sclerosis and albuminuria are strong cardiovascular risk factors and they are both thought to be markers of atherosclerosis. In the LIFE study we investigated the predictive value of AV sclerosis for the composite endpoint (CEP) of cardiovascular death, non-fatal stroke or non-fatal myocardial infarction correcting for urine albumin/creatinine ratio (UACR) and other cardiovascular risk factors.

Methods: After two weeks of placebo treatment, clinical, laboratory, and echocardiographic variables were assessed in 960 hypertensive patients from the LIFE Echo substudy, aged 55-80 (mean 66±7) years, with electrocardiographic LV hypertrophy, and without known AV stenosis. Morning urine albumin and creatinine were measured, and urine albumin-creatinine ratio (UACR) was calculated. Macro- and microalbuminuria were defined as UACR≥35 and 3.5≤UACR<35, respectively. AV sclerosis was defined as valve thickening or calcification. 15 patients with mild AV stenosis were excluded.

Results: AV sclerosis was found in 388 patients and was associated with higher incidence of CEP (15.5% vs. 8.3%**). Micro- and macroalbuminuria were found in 143 (17.1%) and 23 (2.8%) patients, respectively, and both were associated with higher incidence of CEP (15% and 22% vs. 9.9%*). The incidence of CEP increased progressively with micro- and macroalbuminuria in patients without AV sclerosis (11.4% and 15.4% vs. 8.3%*) as well as in patients with AV sclerosis (19.2% and 30% vs. 12.7%*). In Cox regression analyses AV sclerosis was predictive of the CEP (odds ratio [OR] = 1.6*) independent of log UACR (1.5*); male gender (2.1**); and history of peripheral vascular disease (2.5**), diabetes mellitus (2.3**) or cerebral vascular disease (2.4**). *P<0.05.